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(54) Title: MODIFIED PEPTIDES TRANSPORTABLE INTO THE CENTRAL NERVOUS SYSTEM

(57) Abstract

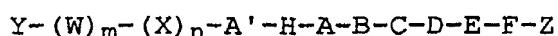
This concerns modified peptides and their pharmaceutically acceptable salts which can effectively penetrate the blood-brain barrier. Also of concern are pharmaceutical compositions containing these peptides and methods of treatment using such compositions.

CLAIMS

What is claimed is:

1. A compound of the formula

5



wherein

Y is a lipophilic moiety having the structure
10 L-C(O)-, or R-(CH₂)_p-C(O)-(CH₂)_r-, provided that when Y
is L-C(O)- then L is selected from the group consisting
of (i) at least one alkyl group having 1-16 carbon
atoms, said alkyl group can be branched or unbranched,
unsubstituted or substituted with at least one cyclic
15 moiety selected from the group consisting of a
cycloalkyl group having 3-8 carbon atoms, a heterocyclic
group having 5-7 atoms in which the heteroatom is N, O,
or S, or an aryl group having 6-15 carbon atoms wherein
said aryl group can be unsubstituted or substituted with
20 at least one alkyl group having 1-4 carbon atoms, (ii)
perfluoroalkyl having 1-10 carbon atoms which can be
unsubstituted or substituted with at least one cyclic
group selected from the group consisting of an aryl
group having 6-10 carbon atoms, a cycloalkyl group
25 having 3-8 carbon atoms, or a heterocyclic group having
5-7 atoms in which the heteroatom is N, O, or S, (iii)
cycloalkyl having 3-8 carbon atoms, (iv) bicycloalkyl
having 6-18 carbon atoms, (v) tricycloalkyl having 6-18
carbon atoms, (vi) R¹-NH-R² wherein R¹ is H or alkyl
30 having 1-4 carbon atoms; R² is selected from the group
consisting of alkanediyl, branched or unbranched, having
1-16 carbon atoms, unsubstituted or substituted with at
least one cyclic group selected from the group
consisting of cycloalkyl having 3-8 carbon atoms,
35 heterocyclic having 5-7 atoms in which the heteroatom is

- N, O, or S, or an aryl group having 6-15 carbon atoms unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms, alkylcycloalkyl branched or unbranched having 4-16 carbon atoms wherein the
- 5 cycloalkyl group has 3-8 carbon atoms, cycloalkylalkyl branched or unbranched having 4-16 carbon atoms wherein the cycloalkyl group has 3-8 carbon atoms, alkylaryl substituted with at least one moiety selected from the group consisting of alkyl, branched or unbranched,
- 10 having 7-16 carbon atoms, said alkyl group being unsubstituted or substituted with NHR¹ or OH, said aryl group being unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms, arylalkyl substituted with at least one moiety selected from the
- 15 group consisting of alkyl, branched or unbranched, having 7-16 carbon atoms, said alkyl group being unsubstituted or substituted with NHR¹ or OH, said aryl group being unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms, or
- 20 alkylheterocyclic substituted with an alkyl group, branched or unbranched, having 6-16 carbon atoms, said heterocyclic having 5-7 atoms in which the heteroatom is N, O, or S,
- further provided that when Y is R-(CH₂)_p-C(O)-
- 25 (CH₂)_r- then R is a cyclic group selected from the group consisting of cycloalkyl having 3-8 carbon atoms, heterocyclic having 5-7 atoms in which the heteroatom is N, O, S, or heterocyclic having 5-7 atoms in which the heteroatom is N and said heterocycle has at least one
- 30 carbonyl moiety adjacent to the heteroatom, or aryl having 6-15 carbon atoms unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms; p and r are independently integers from 0 to 6;
- W is an amino acid residue selected from the group
- 35 consisting of arginine, lysine, ornithine, homoarginine,

2,4-diaminobutyric acid, 2,3-diaminopropionic acid, norleucine, N-methylnorleucine, D-arginine, D-lysine, proline, and 4-aminocyclohexylalanine.

X is an amino acid residue selected from the group
5 consisting of arginine, lysine, ornithine, homoarginine,
2,4-diaminobutyric acid, 2,3-diaminopropionic acid,
norleucine, N-methylnorleucine, D-arginine, D-lysine,
proline, 4-aminocyclohexylalanine, alanine, or an alpha-
amino acid residue substituted at the alpha carbon with
10 at least one alkyl group having 1-6 carbon atoms, or
said alpha-carbon atom is part of a cyclic moiety
selected from the group consisting of cycloalkyl having
3-8 carbon atoms or heterocyclic having 3-8 atoms in
which the heteroatom is N, O, or S;

15 m and n are independently 0 or 1, provided that m
and n are not both 0 unless L is R¹-NH-R²;

A', A, C, and E are independently selected from the
group consisting of -CONH-, -CON(CH₃)-, -N(CH₃)CO-,
-NHCR'R"-, -CR'R"NH-, -SO₂NR'R"-, -NR'R"SO₂-, -CH₂NH-,
20 -CH₂O-, -CH₂S-, -NHCH₂-, -OCH₂-, -CSNH-, -NHCONH-,
-S(O)CH₂-, -S(O)₂CH₂-, -NHSC-, -CH₂S(O)-, -CH₂S(O)₂-,
-SCH₂-, cis- or trans- -CH=CH-, -NHCO-, -CH₂CH₂-,
-CF₂CF₂-, -CF=CF-, -CF=CH-, -CH=CF-, -COCH₂-, -CH₂CO-,
-CH(OH)CH₂-, -CH₂CH(OH)-, 1,2-cyclopropyldiyl, and
25 4,5-tetrazolyldiyl, wherein R' and R'' are independently
lower alkyl groups having 1-6 carbon atoms;

H is an amino acid residue selected from the group
consisting of proline or N-methylaminobutyric acid;

B is an amino acid residue selected from the group
30 consisting of tyrosine, phenylalanine, tryptophan,
naphthylalanine, phenylglycine, and beta-phenylproline;

D is an amino acid residue selected from the group
consisting of isoleucine, leucine, tert-leucine, and
phenylglycine;

F is an amino acid residue selected from the group consisting of leucine, valine, and methionine; and Z is OH or OR³ wherein R³ is an alkyl group having 1-6 carbon atoms.

- 5 2. A compound according to claim 1 wherein Y is a lipophilic moiety having the structure L-C(O)- or R-(CH₂)_p-C(O)-(CH₂)_r-, provided that when Y is L-C(O)- then L is selected from the group consisting of (i) alkyl, branched or unbranched, having 1-16 carbon atoms, (ii)
- 10 perfluoroalkyl having 1-10 carbon atoms, (iii) cycloalkyl having 3-8 carbon atoms, (iv) bicycloalkyl having 6-18 carbon atoms, (v) tricycloalkyl having 6-18 carbon atoms, (vi) R¹-NH-R²- wherein R¹ is H or alkyl having 1-4 carbon atoms, R² is selected from the group
- 15 consisting of alkanediyl, branched or unbranched having 1-16 carbon atoms, alkylaryl substituted with at least one moiety selected from the group consisting of alkyl, branched or unbranched, having 7-16 carbon atoms, said alkyl group being unsubstituted or substituted with NHR¹
- 20 or OH, said aryl group being unsubstituted or substituted with at least alkyl group having 1-4 carbon atoms, or arylalkyl substituted with at least one moiety selected from the group consisting of alkyl, branched or unbranched, having 7-16 carbon atoms, said alkyl group
- 25 being unsubstituted or substituted with NHR¹ or OH, said aryl group being unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms;
- further provided that when Y is R-(CH₂)_p-C(O)-(CH₂)_r- then R is a cyclic group selected from the group
- 30 consisting of cycloalkyl having 3-8 carbon atoms, aryl having 6-15 carbon atoms unsubstituted or substituted with at least one alkyl group having 1-4 carbon atoms, heterocyclic having 5-7 atoms in which the heteroatom is N, O, or S, or heterocyclic having 5-7 atoms in which
- 35 the heteroatom is N and said heterocycle has at least

one carbonyl moiety adjacent to the heteroatom; p and r are independently integers from 0 to 6;

W is an amino acid residue selected from the group consisting of arginine, lysine, ornithine, 2,4-
5 diaminobutyric acid, norleucine, N-methylnorleucine, D-arginine, 4-aminocyclohexylalanine, or proline;

X is an amino acid residue selected from the group consisting of arginine, lysine, ornithine, 2,4-
diaminobutyric acid, norleucine, N-methylnorleucine, D-
10 arginine, proline, 4-aminocyclohexylalanine, alanine, or an alpha-amino acid residue in which the alpha carbon is part of cyclic moiety selected from the group consisting of cycloalkyl having 3-8 carbon atoms or heterocyclic having 3-8 atoms in which the heteroatom is N, O, or S;
15 m and n are independently 0 or 1, provided that m and n are not both 0 unless L is R¹-NH-R²;

A', A, C, and E are independently selected from the group consisting of -CONH-, -CH₂NH-, -CH₂O-, -CH₂S-, -NHCH₂-, -OCH₂-, -CSNH-, -NHSC-, -SCH₂-, cis- or trans-
20 -CH=CH-, -NHCO-, -CH₂CH₂-, -CF₂CF₂-, -CF=CF-, -CF=CH-, -CH=CF-, -COCH₂-, -CH₂CO-, -CH(OH)CH₂-, -CH₂CH(OH)-;

H is an amino acid residue selected from the group consisting of proline or N-methylaminobutyric acid;

B is an amino acid residue selected from the group consisting of tyrosine, phenylalanine, tryptophan, naphthylalanine, phenylglycine, and beta-phenylproline;

D is an amino acid residue selected from the group consisting of isoleucine, leucine, tert-leucine, and phenylglycine;

30 F is an amino acid residue selected from the group consisting of leucine, valine, and methionine; and

Z is OH or OR³ wherein R³ is alkyl having 1-6 carbon atoms.

3. A compound according to claim 1 wherein

- Y is selected from the group consisting of acetyl, pivaloyl, neopentylcarbonyl, n-perfluorooctanoyl, 1-bicyclo[3.3.0]octanecarbonyl, 2-bicyclo[2.2.1]heptane-acetyl, 1-adamantanecarbonyl, 2-pyrrolidinecarbonyl 5 (prolyl), 2-(5-pyrrolid-5-one)-carbonyl[pyroglutamyl], benzoyl, 4-tert-butylbenzoyl, 4-phenylbenzoyl, nicotinoyl, 2-benzyl-5-aminopentanoyl, trans-4-(aminomethyl)-cyclohexanecarbonyl, 2-(aminomethyl)-benzoyl, and 4-(aminocyclohexyl)-alanyl;
- 10 W is an arginine residue;
- X is an amino acid residue selected from the group consisting of arginine, lysine, ornithine, 4-aminocyclohexylalanine, 4-aminopiperidine-4-carboxylic acid, 1-aminocyclopentanecarboxylic acid, 1-
- 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 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5225 5230 5235 5240 5245 5250 5255 5260 5265 5270 5275 5280 5285 5290 5295 5300 5305 5310 5315 5320 5325 5330 5335 5340 5345 5350 5355 5360 5365 5370 5375 5380 5385 5390 5395 5400 5405 5410 5415 5420 5425 5430 5435 5440 5445 5450 5455 5460 5465 5470 5475 5480 5485 5490 5495 5500 5505 5510 5515 5520 5525 5530 5535 5540 5545 5550 5555 5560 5565 5570 5575 5580 5585 5590 5595 5600 5605 5610 5615 5620 5625 5630 5635 5640 5645 5650 5655 5660 5665 5670 5675 5680 5685 5690 5695 5700 5705 5710 5715 5720 5725 5730 5735 5740 5745 5750 5755 5760 5765 5770 5775 5780 5785 5790 5795 5800 5805 5810 5815 5820 5825 5830 5835 5840 5845 5850 5855 5860 5865 5870 5875 5880 5885 5890 5895 5900 5905 5910 5915 5920 5925 5930 5935 5940 5945 5950 5955 5960 5965 5970 5975 5980 5985 5990 5995 6000 6005 6010 6015 6020 6025 6030 6035 6040 6045 6050 6055 6060 6065 6070 6075 6080 6085 6090 6095 6100 6105 6110 6115 6120 6125 6130 6135 6140 6145 6150 6155 6160 6165 6170 6175 6180 6185 6190 6195 6200 6205 6210 6215 6220 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7225 7230 7235 7240 7245 7250 7255 7260 7265 7270 7275 7280 7285 7290 7295 7300 7305 7310 7315 7320 7325 7330 7335 7340 7345 7350 7355 7360 7365 7370 7375 7380 7385 7390 7395 7400 7405 7410 7415 7420 7425 7430 7435 7440 7445 7450 7455 7460 7465 7470 7475 7480 7485 7490 7495 7500 7505 7510 7515 7520 7525 7530 7535 7540 7545 7550 7555 7560 7565 7570 7575 7580 7585 7590 7595 7600 7605 7610 7615 7620 7625 7630 7635 7640 7645 7650 7655 7660 7665 7670 7675 7680 7685 7690 7695 7700 7705 7710 7715 7720 7725 7730 7735 7740 7745 7750 7755 7760 7765 7770 7775 7780 7785 7790 7795 7800 7805 7810 7815 7820 7825 7830 7835 7840 7845 7850 7855 7860 7865 7870 7875 7880 7885 7890 7895 7900 7905 7910 7915 7920 7925 7930 7935 7940 7945 7950 7955 7960 7965 7970 7975 7980 7985 7990 7995 8000 8005 8010 8015 8020 8025 8030 8035 8040 8045 8050 8055 8060 8065 8070 8075 8080 8085 8090 8095 8100 8105 8110 8115 8120 8125 8130 8135 8140 8145 8150 8155 8160 8165 8170 8175 8180 8185 8190 8195 8200 8205 8210 8215 8220 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9225 9230 9235 9240 9245 9250 9255 9260 9265 9270 9275 9280 9285 9290 9295 9300 9305 9310 9315 9320 9325 9330 9335 9340 9345 9350 9355 9360 9365 9370 9375 9380 9385 9390 9395 9400 9405 9410 9415 9420 9425 9430 9435 9440 9445 9450 9455 9460 9465 9470 9475 9480 9485 9490 9495 9500 9505 9510 9515 9520 9525 9530 9535 9540 9545 9550 9555 9560 9565 9570 9575 9580 9585 9590 9595 9600 9605 9610 9615 9620 9625 9630 9635 9640 9645 9650 9655 9660 9665 9670 9675 9680 9685 9690 9695 9700 9705 9710 9715 9720 9725 9730 9735 9740 9745 9750 9755 9760 9765 9770 9775 9780 9785 9790 9795 9800 9805 9810 9815 9820 9825 9830 9835 9840 9845 9850 9855 9860 9865 9870 9875 9880 9885 9890 9895 9900 9905 9910 9915 9920 9925 9930 9935 9940 9945 9950 9955 9960 9965 9970 9975 9980 9985 9990 9995 9999

X is an amino acid residue selected from the group consisting of arginine, lysine, and ornithine;

m and n are independently 0 or 1, provided that m and n are not both zero, except when Y is 1-benzyl-5-aminopentanoyl then m and n can be zero, and further provided that when Y is acetyl, both m and n are 1;

A', A, C, and E are -CONH-;

H is a proline residue;

B is an amino acid residue selected from the group consisting of tyrosine and tryptophan;

D is an amino acid residue selected from the group consisting of isoleucine, tert-leucine, and phenylglycine;

F is a leucine residue;

Z is OH or OCH₃.

5. A compound according to claim 1 wherein Y is selected from the group consisting of 1-adamantanecarbonyl, 2-norbornaneacetyl, 1-perfluorooctanoyl;

20 W is an amino acid residue selected from the group consisting of Arg, Lys, Orn;

X is an amino acid residue selected from the group consisting of Arg, Lys, Orn, 1-aminocyclopentane-1-carbonyl, 2-, 3-, or 4-amino-piperidine-2-, 3-, or 4-carbonyl;

25 m and n are independently 0 or 1 provided that m and n are not both 0;

A, C, and E are independently -CO-NH-, -CH₂NH-, or trans-CH=CH;

30 B is an amino acid residue selected from the group consisting of Tyr, Phe, Trp;

D is amino acid residue selected from the group consisting of Ile, Leu, Pgl, Gly;

35 F is an amino acid residue selected from the group consisting of Leu, Val; and

Z is OH or OCH₃.

6. A compound according to claim 1 wherein

Y is 1-adamantanecarbonyl;

W and X are independently Arg or Lys;

5 m and n are independently 0 or 1 provided that m
and n are not both 0;

A, C and E are independently -CONH-, -CH₂NH-, or
trans-CH=CH-;

B is Tyr;

10 D is Ile;

F is Leu; and

Z is OH or OCH₃.

7. A compound according to claim 1 which is
selected from the group consisting of:

15 N^α-(1-adamantanecarbonyl)-Arg-Pro-Tyr-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Arg-Arg-Pro-Tyr-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Lys-Pro-Tyr-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Lys-Pro-Ψ[CH₂NH]-Tyr-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Lys-Pro-Ψ[CH=CH]-Tyr-Ile-Leu;

20 N^α-(cis-bicyclo(3.3.0)octane-2-carbonyl)-Lys-Pro-Tyr-
Ile-Leu;

N^α-(1-adamantanecarbonyl)-Orn-Pro-Tyr-Ile-Leu;

N^α-(1-adamantanecarbonyl)-Lys-Pro-Trp-Ile-Leu;

25 N^α-(1-adamantanecarbonyl)-Lys-Pro-Tyr-(S)-2-
phenylglycyl-Leu;

N^α-(2-norbornaneacetyl)-Lys-Pro-Tyr-Ile-Leu;

N^α-(CF₃(CF₂)₆CO)-Lys-Pro-Tyr-Ile-Leu;

4-(1'-adamantanecarbamido)-4-piperidine-carbonyl-Pro-
Tyr-Ile-Leu;

30 N^α(1-adamantanecarbonyl)Lys-Pro-Tyr-Ile-Leu(OMe);

N^α(nicotinoyl)Lys-Pro-Tyr-Ile-Leu;

N^α(Boc)Orn-Pro-Ψ[CH₂NH]Tyr-Ile-Leu;

N^α(Boc)Orn-Pro-TyrΨ[CH₂NH]-Ile-Leu;

N^α(Boc)Orn-Pro-TyrΨ[CH=CH]-Ile-Leu;

35 N^α(Boc)Orn-Pro-Ψ[CH=CH]-Tyr-Ile-Leu;

N^α-(PhCO)-Lys-Pro-Tyr-Ile-Leu;
N^α(t-BuCO)-Lys-Pro-Tyr-Ile-Leu;
N^α-(t-BuCH₂CO)-Lys-Pro-Tyr-Ile-Leu;
N^α-(4-Ph-C₆H₄-CO)-Lys-Pro-Tyr-Ile-Leu;
5 N^α-(4-t-Bu-C₆H₄-CO)-Lys-Pro-Tyr-Ile-Leu;
N-(2-benzyl-5-aminopentanoyl)-Pro-Tyr-Ile-Leu;
N^α-(1-adamantanecarbonyl)-Arg-Arg-Pro-Tyr-Tle-Leu;
N^α-acetyl-Arg-Arg-Pro-Tyr-S-2-phenylglycyl-Leu; or
N^α-(1-adamantanecarbonyl)-Lys-Pro-Tyr-Tle-Leu.

10 8. A pharmaceutical composition comprising a suitable pharmaceutical carrier and an antipsychotic amount of a compound of claims 1-7.

9. A method of treating psychosis in a mammal which comprises administering to the mammal an 15 antipsychotic effective amount of a compound of claims 1-7.

10. A method of treating pain in a mammal which comprises administering to the mammal an analgesic effective amount of a compound of claims 1-7.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/04968

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07K7/08; C07K7/02; C07K5/02; A61K37/02

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.Cl. 5	C07K ; A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ^a	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 333 071 (EISAI CO.) 20 September 1989 cited in the application see the whole document ----	1-10
X	US,A,4 425 269 (CHRISTY ET AL.) 10 January 1984 cited in the application see examples 1-7 ----	1-10 -/-

^b Special categories of cited documents :¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "T" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

07 OCTOBER 1992

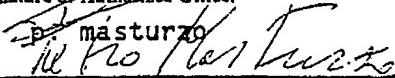
Date of Mailing of this International Search Report

02. 11. 92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer



III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	BIOCHEMICAL PHARMACOLOGY vol. 36, no. 6, 1987, GB pages 869 - 874 K S KANBA ET AL. 'comparison of the stimulation of inositol phospholipid hydrolysis and of cGMP formation by neuropeptides, some of its analogs and neuromedin N in neuroblastoma clone NIE-115' see table 1 ---	1-10
P,X	203RD ACS NAT. MEETING, S. FRANCISCO, CALIFORNIA, APRIL 5-10, 1992, ABSTRACT PAPERS: ABSTRACT NO. 84 vol. 203, no. 1-3, G A CAIN ET AL. 'neurotensin based analgesic identification of minimally active fragment : enhancement of potency, duration of action, and transport properties' see the whole document ---	1-10
P,X	203RD ACS NAT. MEETING, S. FRANCISCO, CALIFORNIA, APRIL 5-10, 1992, ABSTRACT PAPERS, ABSTRACT NO 81 vol. 203, no. 1-3, W K SCHMIDT ET AL. 'adamantoyl-lys-pro-tyr-ile-leu, ada-kypil, a systematically active neuropeptide 9-13 analog with analgesic and antipsychotic profile in mice and rats' see the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/04968

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9-10 refers to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see annex.
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

In view of the extremely large number of compounds falling under claim 1 and 2, and of the absence of any sensible support for these claims in the description, the Search division considers that it is not economically reasonable to draw a search report covering the entire subject matter of claims 1,2 and dependant claims 8 to 10. The search report has therefore been limited to claims 3 to 7, to claims 8- 10 as far as they are dependent from claims 3 to 7 and includes all the real examples given in the description.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9204968
SA 61818**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 07/10/92

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
EP-A-0333071	20-09-89		AU-A- 3108389 JP-A- 1316399	14-09-89 21-12-89
US-A-4425269	10-01-84		None	